AMENDMENT

1. (Original) An isolated cDNA molecule comprising the nucleotide sequence disclosed in SEQ ID NO:3.

2. (Original) An isolated cDNA molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:4; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:3 or the complement thereof.

3. (Original) An isolated recombinant expression vector comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4.

4. (Cancelled)

5. (New) The isolated recombinant expression vector of claim 3, wherein said nucleotide sequence comprises SEQ ID NO:3.

6. (New) A host cell comprising the recombinant expression vector of claim 3.

7. (New) The host cell of claim 6, wherein said recombinant expression vector comprises the nucleotide sequence of SEQ ID NO:3.

RESPONSE

I. Restriction Requirement

The Examiner has determined that the original claims are directed to two separate and distinct inventions under 35 U.S.C. § 121, as follows:

Group I: Claims 1-3, said to be drawn to cDNA molecules and expression vectors, classified in class 435, subclass 320.1; and

Group II: Claim 4, said to be drawn to an isolated protein, classified in class 530, subclass 350.

II. Response to Restriction Requirement

In response to the Restriction Requirement, Applicants hereby confirm the election without traverse, made by Applicants' representative David Hibler during a telephone conference with the Examiner on January 20, 2004, to prosecute the claims of Group I invention (claims 1-3), drawn to cDNA molecules and expression vectors, classified in class 435, subclass 320.1. Accordingly, claim 4 has been cancelled without prejudice and without disclaimer as being drawn to a non-elected invention.

Applicants reserve the right to refile claims to the non-elected invention in one or more future applications retaining the priority date of the present case and the earlier cited priority applications.

III. Status of the Claims

Claim 4 has been cancelled without prejudice and without disclaimer as being drawn to a non-elected invention. No claims of the Group I invention have been cancelled. No claims of the Group I invention have been amended. New claims 5-7 have been added.

Claims 1-3 and 5-7 are therefore presently pending in the case.

IV. Support for the Newly Added Claims

Claim 5 has been added to specifically recite an isolated recombinant expression vector comprising the nucleotide sequence of SEQ ID NO:3. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 14, lines 13-19, and in claim 3 as originally filed.

Claims 6 and 7 have been added to specifically recite host cells comprising the recombinant expression vector of claims 3 and 5, respectively. Support for these claims can be found throughout

the specification as originally filed, with particular support being found at least at page 14, lines 19-25.

It will be understood that no new matter is included within the newly added claims.

V. Rejection of Claims 1-3 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The Examiner states that the presently claimed nucleotide sequences do not have a patentable utility because "(a) search of the sequence database did not reveal any sequences that were 100% identical to the claimed polynucleotides", and "(t)herefore, there appears to be no well-established utility for the claimed polynucleotides" (the Action at page 4). Applicants respectfully point out that not only is this argument completely and totally flawed on a number of different levels, it has absolutely nothing whatsoever to do with the standard for patentability under 35 U.S.C. § 101. Applicants readily agree that no "sequences that were 100% identical to the claimed polynucleotides" are present in the prior art, since such a sequence would completely anticipate the present invention. Applicants respectfully point out that no rejection under any subsection of 35 U.S.C. § 102 has been entered against the present claims, confirming this fact. Additionally, Applicants respectfully point out that the United States Patent and Trademark Office ("the USPTO") does not require 100% identity between nucleotide sequences to establish a patentable utility under 35 U.S.C. § 101. Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit A**), the same Guidelines cited by the Examiner repeatedly in the Action, clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section VI, below), is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score greater than 95% to a protein having a "well established utility". Thus, the Examiner's argument is completely without merit, and in no way whatsoever supports the allegation that the presently claimed invention lacks a patentable utility.

Furthermore, Applicants respectfully point out that the presently claimed sequences shares greater than **98% identity** at the amino acid level over the entire length of SEQ ID NO:3 with two sequences that are present in the leading scientific repository for biological sequence data (GenBank), which have been annotated by independent third party scientists *wholly unaffiliated with Applicants* as CD109 (GenBank accession numbers AF410459 and AY149920, alignments and GenBank reports

provided in **Exhibit B**), which was annotated by both groups of investigators to be a member of the alpha macroglobulin family of proteins (Lin *et al.*, *Blood* **99**:1683-1691, 2002 ("Lin"), and Solomon *et al.*, *Gene* **327**:171-183, 2004 ("Solomon"); abstracts provided in **Exhibit C**). Additionally, CD109 has long been known to express the Gov alloantigen system, which has been associated with neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transfusion purpura (Kelton *et al.*, *J. Lab. Clin. Med.* **132**:142-148, 1998, and Berry *et al.*, *Br. J. Haematol.* **110**:735-742, 2000; abstracts provided in **Exhibit D**). Applicants point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given all of these GenBank annotations and publications, there can be **no question** that those skilled in the art would clearly believe that Applicants' sequence is an alpha macroglobulin protein, exactly as asserted by Applicants in the specification as originally filed (see at least the title of the application, and page 20, lines 4-6), and would therefore have numerous uses, including those detailed below. Therefore, as the present situation **exactly** tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (see **Exhibit A**), the USPTO's **own** examination guidelines clearly indicate that the present claims meet the requirements of 35 U.S.C. § 101.

The Examiner next states that "a sequence search did not reveal any sequences identical or related to SEQ ID NO:3 of the present invention that were known at the time of the invention", and "(t)herefore, at the time of the invention the art did not teach or suggest that the proteins encoded by the polynucleotides with similar sequence to SEQ ID NO:3 were related to any disease or disorder" (the Action at page 6). First, Applicants point out that whether or not "SEQ ID NO:3 were related to any disease or disorder" is not the standard for patentability under 35 U.S.C. § 101 (*In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995)). Second, Applicants respectfully point out that whether or not the references cited by Applicants above were available at the time of filing of the present application is completely and totally irrelevant with regard to the utility issue at hand. Applicants point to the Lin and Solomon references **not** to evidence that these sequences were known in the art at the time the present application was filed, but, rather, to evidence that other skilled artisans have **confirmed** Applicants' assertion that the presently claimed sequence is an alpha macroglobulin protein. Thus, this argument by the Examiner also in no way supports the alleged lack of utility.

It has been well established that Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In*

re Gottlieb, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), and, thus, any questions concerning whether or not the present claims meet the requirements of 35 U.S.C. § 101 have already been laid to rest. Nevertheless, the present invention has a number of additional substantial and credible utilities, not the least of which is in forensic biology, as described in the specification, at least at page 3, line 11. The Examiner questions this asserted utility, stating that "there is no evidence that the claimed polynucleotides have sequences that vary from person to person that would allow such an identification" (the Action at page 7). Applicants respectfully disagree, and point out that as described in the specification at page 17, lines 5-17, the present sequence defines a **number** of coding single nucleotide polymorphisms. Polymorphisms are **by definition** "sequences that vary from person to person". As such polymorphisms are the basis for forensic analysis, which is undoubtedly a "real world" utility, the present sequences must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner further questions this asserted utility because "neither the Specification nor the art of record disclose any diseases or conditions related to the proteins encoded by the polynucleotides of the invention" (the Action at page 5). First, as detailed above, CD109 has long been known to express the Gov alloantigen system, which has been associated with neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transfusion purpura (see **Exhibit D**). Second, Applicants once again point out that the identification of "any diseases or conditions related to the proteins encoded by the polynucleotides of the invention" is not the standard for patentability under 35 U.S.C. § 101 (*In re Brana, supra*). Third, Applicants respectfully point out that the use of the presently described polymorphisms in forensic analysis does **not** require the identification of a specific medical condition. One aspect of forensic analysis is to distinguish individual members of the human population from one another based solely on the **presence** or **absence** of a polymorphic marker, such as the presently described polymorphisms. As polymorphic markers such as the presently described polymorphisms have been used in forensic analysis for decades, this is clearly a well established technique, and as such, specific guidance does not need to be provided in the present specification, for it has long been established that a patent need not disclose what is well known in the art (*In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988)). This is also not a case of a "potential" utility. Using the polymorphic markers exactly as described in the specification as originally filed, the skilled artisan can in fact distinguish individuals from one another. Applicants point out that in the worst case

scenario, each marker is useful to distinguish 50% of the population (in other words, a marker being present in half of the population). This is an inherent feature of any polymorphic marker, as the largest percentage of a population that two polymorphic markers can define is 50% each. If a polymorphic marker is present at a level of less than 50%, then that marker is even **more** informative, *i.e.*, a **greater** percentage of the population can be distinguished on the basis of the marker. Nevertheless, the ability to eliminate even 50% of the population from a forensic analysis clearly is a real world, practical utility.

The Examiner next states that "(a) 'substantial' utility is a utility that defines a 'real world' use" (the Action at page 4). Applicants respectfully point out that naturally occurring genetic polymorphisms such as those described in the specification as originally filed are both the basis of, and critical to, *inter alia*, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on polymorphisms such as those identified by Applicants is used to positively identify or rule out suspects in many criminal cases, and in identifying human remains. Paternity determination is based on polymorphisms such as those identified by Applicants to positively identify or rule out individuals suspected of fathering a particular child. What could be possibly be more "substantial" and "real world" than the loss of an individual's freedom or life through incarceration? What could be possibly be more "substantial" and "real world" than the positive identification of human remains? What could be possibly be more "substantial" and "real world" than the impact, both economic and emotional, that the results of a paternity analysis has on the individuals directly and indirectly involved? These are all well known and generally accepted uses of polymorphisms such as the polymorphisms identified by Applicants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Therefore, as the use of the presently described polymorphic markers in forensic analysis is clearly a "substantial" and "real world" utility, the presently claimed sequences meet the requirements of 35 U.S.C. § 101.

The Examiner further questions this asserted utility, stating that "further research would be required to reasonably confirm or identify how the polynucleotides could be used in such assays" (the Action at page 7). Applicants reiterate that the use of the presently described polymorphic markers in forensic analysis, as detailed above, requires **no** further research. The presently described polymorphisms can be used to distinguish individuals from one another in their presently available form. Furthermore, Applicants take this opportunity to note that throughout the Action the Examiner repeatedly cites the need for "further research" (the Action at pages 4, 5 (twice), and 7) to support the allegation that the present invention lacks a patentable utility. Applicants respectfully point out that the

proper standard for meeting the requirements of 35 U.S.C. § 101 is **not** whether "further research" is required to practice certain aspects of the claimed invention, but whether **undue** experimentation would be required to practice the claimed invention. The widespread use of polymorphisms such as that described by Applicants in forensic analysis every day **strongly** argues against such a use requiring "undue experimentation". Applicants reiterate that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Thus, the Examiner's argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner goes on to state that this asserted utility is "not considered specific" because "any nucleic acid molecule could be used" in this fashion, and thus the utility is considered "general" (the Action at page 4). Applicants first point out that not all nucleic acids contain polymorphic markers. In fact, the basis for forensic analysis is the fact that such polymorphic markers are not present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Second, until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is meaningless. Third, the Examiner appears to be confusing the requirement for a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a unique utility, which is clearly an improper standard. As set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not **other** nucleic acid sequences contain polymorphic markers and can thus be used in forensic analysis is completely irrelevant to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every**

nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in the *Carl Zeiss* case is mandatory legal authority that essentially controls the outcome of the present case. This case, and particularly the cited quote, directly rebuts the Examiner's argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the USPTO. If every invention were required to have a unique utility, the USPTO would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Throughout the Action, the Examiner attempts to **narrowly** define the "general" class of the invention to include **only** those members that share the asserted utility, and then state that the asserted utility is "general". Applicants respectfully point out that the "general" class with regard to the present invention is **all** nucleic acids. Applicants reiterate that **not** all nucleic acids contain polymorphisms. Therefore, the question of whether the asserted utility is "specific", as opposed to "general", has **clearly** been laid to rest. Applicants note that the "general" class of the invention cannot be redefined to include **only** those nucleic acids that contain polymorphic markers, as the Examiner is forced to do in order to support the allegation that the claimed nucleic acids lack a patentable utility. Thus, the Examiner's argument is completely improper and in clear defiance of established case law, and therefore is in no way whatsoever sufficient to overcome Applicants' assertion of utility. Therefore the present claims are clearly in compliance with 35 U.S.C. § 101.

Furthermore, Applicants point out that as the presently described polymorphisms are part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in *In re*

Brana (*supra*; "*Brana*") is directly on point. In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added.

Additionally, it is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person

of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, as the skilled artisan would readily understand that the present polymorphic markers have utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, given the medical relevance of CD109, and thus the presently claimed sequence, as an additional example of the utility of the present nucleotide sequences, the skilled artisan would readily appreciate the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 6, lines 5-7, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits E-J**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO). As the present sequences are specific markers of human chromosome 6 (see below), those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001; **Exhibit K**). The results have

been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001; **Exhibit L**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner states that this "is not considered a substantial utility because it amounts to basic research for studying the properties of the claimed product itself" (the Action at page 7). Given the medical relevance of the presently claimed sequence, as detailed above, the allegation that assessing the gene expression patterns of the presently claimed sequences amounts to no more than "basic research" is misplaced. Regarding the implication that "any nucleic acid molecule" (the Action at page 4) could be so used, Applicants first point out that only expressed sequences can be used to assess gene expression patterns using DNA chips, not just any nucleic acid. Applicants reiterate that the requirements of a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an **improper** standard (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). The fact that other nucleotide sequences are expressed and could thus be used to assess gene expression patterns using DNA chips does not mean that this use of Applicants' sequence is not a specific utility. Once again, the question of whether or not **other** nucleic acid sequences can be so used is completely irrelevant to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is once again an emphatic **no**. Applicants respectfully point out that in this case the Examiner is attempting to narrow the broad class of "any nucleic acid molecule" to include **only** "any cDNA molecule" (the Action at page 5) in order to support the allegation that the claimed nucleic acids lack a patentable utility, which Applicants point out once again is improper under the law as well as the policy of the USPTO. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 1-3, the present nucleotide sequences have a specific utility in "identification of coding sequence" and "mapping a unique gene to a particular chromosome". The Examiner also questions these asserted utilities, stating "the Specification is no more specific that citing chromosome 6", and that "(s)uch is a general statement and does not include specifics such as where

on chromosome 6 one would want to look" (the Action at page 7). Applicants respectfully disagree, and point out that as described in the specification as originally filed at page 3, line 5, the gene encoding the presently claimed sequences is present on "human chromosome 6, see GenBank accession number AC026605". Thus, clearly, the specification as originally filed does include "specifics such as where on chromosome 6 one would want to look", specifically, the region of human chromosome 6 defined by GenBank Accession Number AC026605. In fact, alignment of SEQ ID NO:3 with GenBank accession numbers AL590428 (which replaced GenBank accession number AC026605, see **Exhibit M**) and AL591480 (two overlapping genomic clones from human chromosome 6) shows that the human gene corresponding to the presently claimed sequences is dispersed on 33 exons of human chromosome 6 (alignment and first pages of the GenBank reports are presented in **Exhibit N**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 6 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325; see **Exhibit K**), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants point out that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 3, lines 6-8, the claimed sequences "identify actual, biologically verified, and therefore relevant, exon splice junctions as opposed to those that may have been bioinformatically predicted from genomic sequence alone". The specification also details that

"sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 13-18). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Once again, regarding the implication that "any nucleic acid molecule" (the Action at page 4) could be so used, Applicants first point out that only expressed sequences can be used in the identification of coding sequence, not just any nucleic acid. Applicants reiterate that the requirements of a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an **improper** standard (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 6 does not mean that the use of Applicants' sequence to map the protein coding regions of chromosome 6 is not a specific utility. Once again, the question of whether or not **other** nucleic acid sequences can be so used is completely irrelevant to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is once again an emphatic **no**. Applicants respectfully point out that in this case the Examiner is once again attempting to narrow the broad class of "any nucleic acid molecule" to include **only** "any cDNA molecule" (the Action at page 5) in order to support the allegation that the claimed nucleic acids lack a patentable utility, which Applicants point out once again is improper under the law as well as the policy of the USPTO. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy

35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits O-Q**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples; **Exhibit R**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VI, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid

molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-3 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

VI. Rejection of Claims 1-3 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-3 have been shown to have "a specific, substantial, and credible utility", as detailed in section V above, the present rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. Rejection of Claims 1-3 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse.

The Action states that "(e)ven in the case that the claimed polynucleotides were shown to be supported by a specific and substantial utility, the Specification does not provide support for using the claimed polynucleotides in any methods of treatment or diagnosis or methods of screening for drugs" (Action at page 8). Applicants point out that the above comment is completely irrelevant to determining whether the claimed compositions meet the legal requirements for patentability under 35 U.S.C. § 112, first paragraph. Therefore, Applicants submit that the Examiner has failed to present reasoning sufficient to establish a *prima facie* case supporting the present § 112 rejection, and accordingly the rejection is improper because: 1) the Examiner's comments were not relevant to the established legal standard of enablement; 2) the Examiner's failure to attribute adequate weight and attention to the detailed level of teaching clearly provided in the specification; and 3) the reasoning for the enablement rejection provided by the Examiner failed to adequately consider the high level of technical knowledge that can be attributed to those skilled in the art in the field of the present invention.

In attempting to establish a *prima facie* case to support the § 112 rejection of the composition claims, the Action questions whether the claimed compositions are sufficiently enabled to allow those skilled in the art to practice aspects of the invention involving standard molecular biological techniques. The § 112 rejection, as applied against the nucleic acid compositions, is completely misplaced. It has long been established that composition claims are enabled by defining any practical use of the claimed compound. *In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka, supra.* "The enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991).

The Action seems to contend that the specification provides insufficient guidance regarding the biological function or activity of certain of the claimed compositions. However, such an enablement standard conflicts with established patent law. As discussed in Section V, above, in *In re Brana, supra*, the Federal Circuit admonished the USPTO for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442.

The Examiner states that the present invention could not be practiced without "undue experimentation" (Action at page 11). However, it is important to remember that, as discussed above in Section V, in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin, supra.* In *Wands, supra*, the USPTO took the position that the applicant failed to demonstrate that the disclosed biological processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the USPTO's rejection, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art

> one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., supra.*

Applicants point out that numerous uses of the claimed sequences do not require knowledge of **any** functional aspects of the amino acid sequences. Significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (utilizing, for example, arrays of short, overlapping or non-overlapping, oligonucleotides and DNA chips, as described in Section V, above) to chromosomal mapping (utilizing, for example, short oligonucleotide probes or full length DNA sequences, as described in Section V, above) are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. The widespread commercial exploitation of nucleic acid sequence information points to the level of skill in the art, and the enablement provided by disclosures such as the present specification, which include specific nucleic acid sequences and guidance regarding the various uses of such sequences.

Even though the burden has been improperly shifted to Applicants, the following section is being provided to demonstrate that the specification is fully enabling in view of the detailed guidance and teaching provided in the specification within the context of the high level of technical knowledge present in the art regarding the use of nucleic acids such as those presently claimed.

The Action questions the teaching and guidance in the specification for certain aspects of the present invention. However, as discussed above, this requirement is completely misplaced. There is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further details in a patent specification. For example, it is not unreasonable to expect a Ph.D. level molecular biologist to be able to use the disclosed sequence to design oligonucleotide probes and primers and use them in, for example, PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Nevertheless, the present specification provides highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed

invention, including recombinant expression, site-specific mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques, and properly incorporates by reference a montage of standard texts into the specification, such as Sambrook *et al.* (*Molecular Cloning, A Laboratory Manual*) and Ausubel *et al.* (*Current Protocols in Molecular Biology*) to provide even further guidance to the skilled artisan. Incorporation of material into the specification by reference is proper. *Ex parte Schwarze*, 151 USPQ 426 (PTO Bd. App. 1966). The § 112, first paragraph rejection is thus *prima facie* improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, supra, emphasis as in original. In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra.* In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As standard molecular biological techniques are routine in the art, such protocols do not need to described in detail in the specification.

Furthermore, a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it." *In re Naquin*, 158 USPQ 317, 319 (CCPA 1968); emphasis added. The present claims are thus enabled as they are supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed.

Therefore, as all aspects of the enablement rejection have been overcome, Applicants respectfully request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph be withdrawn.

VIII. Rejection of Claim 2 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 2 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description

of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

The Examiner states that the written description requirement is not satisfied because claim 2 "does not include any limitations on ... the function of the protein it encodes" (the Action at page 11). Applicants respectfully point out that this argument is in direct contradiction of the USPTO Written Description Guidelines (66 Fed. Reg. at 1106). In these Guidelines, the USPTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (66 Fed. Reg. at 1106, emphasis added). The Federal Circuit has recently confirmed this aspect of the USPTO Written Description Guidelines, wherein this exact quote was reproduced (*Enzo Biochem, Inc. v. Gen-Probe, Inc. et al.* (296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002)). Taking the exact statement from the USPTO Written Description Guidelines clause by clause, the written description requirement for a claimed genus may be satisfied through disclosure of sufficiently detailed, relevant identifying characteristics, which are defined as: (a) complete or partial structure; (b) other physical and/or chemical properties; (c) functional characteristics when coupled with a known or disclosed correlation between function and structure; **or** (d) some combination of such characteristics. In other words, the written description requirement is satisfied by (a), (b), (c) **or** (d). Clause (a) states that the written description requirement may be satisfied by the disclosure of structure. The Federal Circuit has held

that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph. Thus, the present claims are in clearly in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

The Examiner states that because "part (b) [of claim 2] is drawn to an isolated cDNA molecule comprising a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO:3 or the complement of the hybridizing cDNA" (the Action at page 11), that claim 2 fails to meet the written description requirement. Applicants respectfully point out that claim 2 requires an isolated cDNA molecule that encodes the amino acid sequence shown in SEQ ID NO:4 **and**

hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:3 or the complement thereof. Therefore, using the sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific **structural** description provided, which is all that is required for compliance with the written description requirement under 35 U.S.C. § 112, first paragraph. Polynucleotides that encode SEQ ID NO:3 **and** hybridize to the nucleotide sequence of SEQ ID NO:3 or the complement thereof under stringent conditions are within the genus of the instant claims, while those that lack this **structural** feature lie outside the genus. Claim 2 thus meets the written description requirement.

Applicants therefore respectfully request that the rejection of claim 2 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IX. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Schnizer have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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Date

David W. Hibler Reg. No. 41,071
Agent for Applicants

CUSTOMER NUMBER
24231

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399